Case Report

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Prenatal Workup of Mucopolysaccharidosis (MPS) III- A Lysosomal Storage Disease

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Abstract

Mucopolysaccharidosis (MPS) are the group of autosomal recessive disorders characterized by deficiency of lysosomal enzymes which break down the glycosaminoglycans (GAGs). Their deficiency results in widespread intra & extra cellular accumulation of GAGs. Diagnosis of MPS is difficult due to rarity of these disorders and variety of clinical manifestation of varied severity. But because of genetic mutations there are high chances of recurrence which can be suspected with the help of family pedigree analysis & diagnosed by the Pre-natal genetic diagnosis (PGD). The purpose of this case is to report the process of follow up for genetic diseases which should always be kept in mind in today's routine obstetric practice when most of pregnancies are occurring after the age of 30 years.

Keywords: Mucopolysaccharidosis (MPS); Prenatal Genetic Diagnosis (PGD); Lysosomal Storage Disease; Sanfilippo Disease; Haparan Sulphate.

Introduction

Mucopolysaccharidosis (MPS) are the group of autosomal recessive disorders characterized by deficiency of lysosomal enzymes responsible for glycosaminoglycans (GAGs) degradation leading to their intra & extra cellular accumulation [1]. GAGs are the main component of connective tissue and the MPS are divided according to enzyme deficiency. MPS are the most common lysosomal storage diseases with incidence of 1: 10,000 births [2]. No body wants to have a debilitated child in the family. Diagnosis of MPS is difficult due to rarity and variety of clinical manifestations. But because of genetic mutations there are high chances of recurrence which can be suspected with the help of family pedigree & diagnosed by the Pre-natal genetic diagnosis (PGD). The purpose of this case is to report the process of follow up for genetic MPS disease.

Case Report

This is the case in which the 35 year old female P1 L 1 A1 presented to antenatal OPD for prenatal counselling with history of first term vaginal delivery of 2.4kg male baby who had delayed milestones and was unable to stand, squat or walk. She wanted to know the cause of such abnormality and prognosis for the future pregnancies.

Work up

Baby did not had any gross facial, extremity or cerebral malformation, had a smooth spontaneous delivery with normal cry in hospital, was breast fed and had no history of fever, seizures or jaundice in early neonatal period but milestones were delayed. On examination had difficulty in standing and walking, cannot even stand without support. Child was well conscious & alert, had hirsutism, coarse features, contractures at fingers, Genu valgus, power at hip was 2/5 while 3/5 at knee. There was abdominal distension with hepato-splenomegaly and small umbilical hernia. Detailed family history & pedigree analysis was done but no such abnormality was there in family in last three generations. There was no history of consanguineous marriage in family. Couple was counselled and asked to get some basic investigations as X-ray thoraco-lumbar spine

(AP & Lateral view) and hand with wrist for the bone age which were within normal limits with osteopenia. Auditary & Ophthalmic examination was also normal.

Suspecting syndrome, Urinary Toludine blue O spot, a screening test for MPS was done which was found to be positive, this was followed by Urine electrophoresis which showed unusual band pattern in the region of chondroitin suphate. Urinary biochemical analysis showed high levels of heparin & haparan sulphate suggesting MPS type III. There are multiple enzymes responsible for degradation of haparan sulphate, for exact diagnosis, she was referred to Sir Ganga Ram Hospital for enzymatic & genetic analysis. Enzymes results were heparan sulfate sulfatase / sulphamidase {0.23nmol/mg/17hr = low} (type A), *N* -acetyl-alpha-D-glucosaminidase {NAG – 49.7nmol/mg/17hr}(type B), alpha-glucosaminide acetyltransferase {26.6nmol/mg/17hr} (type C) and *N*- acetylglucosamine-6-sulfatase {18.5 nmol/mg/24hr} (type D).

Results confirmed MPS III A (Sanfilippo disease) which was followed by gene mapping for mutations. Child was found to be homozygous for p.S69R mutation in the N - sulfoglucosamine sulfohydrolase gene (SGSH) at 17q25.3. MPS III being an autosomal recessive disease couple was advised for carrier testing, and both parents were found to be heterozygous for p.S69R mutation, therefore counselled that they have future 25% chance of recurrence while 50% will be normal and rest 25% will be carrier for the same mutation.

Next year she conceived and was send to Ganga Ram Hospital at 10-11 weeks for the Prenatal genetic diagnostic (PGD) tests for Sanfilippo type III A disease via chorion villous sampling (CVS) in which Haparan sulphamidase was found to be extremely low < 0.062 nmol/mg/17hr and fetal DNA was found to be homozygous for p.S69R mutation on SGSH gene. Pregnancy was terminated as results suggested that the child is going to be affected. After few months she conceived again and was resend for PGD via CVS and this time enzyme heparin suphamidase was 22.4nmol/mg/17hr and fetal DNA was found to be heterozygous for p.S69R mutation suggesting that fetus is a carrier and not likely to suffer therefore pregnancy was allowed to continue.

Discussion

In 1963, mucopolysaccharidosis III, was first reported by pediatrician, Sylvester Sanfilippo and named after him. Sanfilippo syndrome is an autosomal recessive disease & is commonest responsible for 80% of MPS syndromes with incidence of 1 in 70,000 and affects both males & females equally.

Consanguineous marriages are the common reason for the recessive genetic disorders [3].

All the MPS cannot be determined by clinical features alone, precise identification relies on enzymatic assays. Glycosaminoglycan (GAG), haparan sulphate is not metabolized due to deficiency of enzymes and gets accumulated and affect cell function which can be tested from urine biochemical examination & electrophoresis [4]. Type IIIA is the most severe subtype, although neonate is normal at birth but there is developmental delay along with worsening clinical features and has shortest survival [5]. Mental and physical disabilities prevent children from doing well in school. Symptomatology of MPS are varied, however coarse facial features and hirsutism are classic clinical features of Sanfilippo disease. With the advent of molecular biology & gene mapping, genetic mutations responsible for different enzyme deficiencies of MPS type III has been identified as follows [6]:

- Type IIIA - 17q25.3 - Heparan sulfate sulfatase
- Type IIIB - 17q21.2 - *N*-acetyl-alpha-D-glucosaminidase NAG
- Type IIIC - 8p11.21 - Alpha-glucosaminide acetyltransferase
- Type IIID - 12q14.3 - *N*-acetylglucosamine-6-sulfatase-

Location	Phenotype	Inheritance	Phenotype MIM no.	Phenotype map key	Gene/Locus	Gene MIM no.
17q25.3	MPS IIIA	Autosomal Recessive	252900	3	SGSH	605270

First step of workup is history, 3 generation pedigree and clinical examination. Urine analysis is the best screening test for cases suspected of MPS. Ideally, first morning urine sample should be tested because it has highest concentration of substrates. Common GAG tested are, Heparan sulphate (HS), Dermatan sulphate (DS) and Chondroitin sulphate (CS) etc. Lysosomal enzymes can be measured for confirmation from the blood leucocytes or for prenatal genetic diagnosis (PGD) from cultured amniocytes or

chorionic villous tissue.

Genetic analysis of the affected child and parents should be identified for prognostic purpose [7]. Qualitative analysis of cell-free amniotic fluid offers the advantage of being a rapid & sensitive method, eliminating the culture for amniocytes as fetal urine is a major contributor to the formation of amniotic fluid from mid-pregnancy [8].

Management

Medications are used for symptomatic treatment, such as anticonvulsants for seizures and sedatives to improve their quality of sleep. Other advanced options are Bone marrow replacement (BMT) [9], Enzyme replacement therapy (ERT) and substrate reduction therapy (SRT) as Genistein derivative which inhibits synthesis of GAGs. Exercises to limit the progressive loss of motion.

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